CHAPTER I

INTRODUCTION

The selective oxidation is one of fundamental reactions in functional group transformations in organic synthesis. There have been many researches on this oxidation, especially the research for versatile and selective reagents and catalysts. The vast majority catalysts used in modern chemical industry are based on transition metals but almost of all are harmful and toxic. For example, the most widely used and powerful readily available are chromium compounds such as chromic acid, chromium trioxide/H_2SO_4 (Jones reagent), pyridinium chromiumtrioxide /pyridine complex (Collins reagent), pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC). Unfortunately, these are hazardous oxidizing agents; therefore, environmental and health concerns limit their use for large scale and industrial applications; moreover, some reactions required vigorous conditions such as high pressure and/ or high temperature. For these reasons, there are several oxidation reactions employing practical and low-cost catalysts have been developed. In this thesis, the oxidation of organic model substrates using chromium complexes as catalysts in order to mediate functional group transformations and study their selectivities in order to apply to use for oxidation natural products. It has been observed that substrates are oxidized by *tert*-butyl hydroperoxide (TBHP), in the presence of chromium complexes, to give corresponding aldehydes and ketones in moderate and high yield. In addition, this oxidation reaction affords a useful technique for transforming the available raw materials under mild condition.

1.1 Chromium-catalyzed oxidation

As a typical transition metal, chromium has the ground state electronic configuration $1s^2 2s^2 2p^6 3s^2 3p^6 3d^5 4s^1$. Chromium compounds exist in an unusually large

number of oxidation states (0 to +VI). The most common oxidation states of chromium in inorganic compounds are +II, +III, and +VI. Complexes of divalent chromium are usually strongly reducing and are often prone to air oxidation. The most stable oxidation state of the element is +III and the largest amount of its coordination compounds exist in this state. Chromium (IV) and chromium(V) species are, however, important in chromium(VI) induced oxidations, since they always occur as the intermediates. In its highest oxidation state (+VI) chromium forms compounds which are all oxo compounds, but the number of complexes representing it is rather limited. Chromium oxidations have been widely explored and are still of interest due to the wide variety of oxidizable functions by the proper choice of reagents. A large number of chromium reagents and procedures have been described above. These methods imply either the use of stoichiometric quantities or large excess of chromium reagents. In addition, the metallic by-products are also toxic and their presences make the reaction work-up cumbersome. Due to the above cost and environmental factors, it is advantageous to use chromium-catalyzed oxidation instead [1].

## 1.2 Chromium(0) as catalyst

Only chromium carbonyl complexes have been employed as catalysts in order to use for oxidation of organic compounds.

1.2.1 Chromium hexacarbonyl complex, Cr(CO)$_6$

The Cr(CO)$_6$, chromium hexacarbonyl complexes have been used as chromium(0) catalysts for the oxidation of allylic and benzylic oxidations to the corresponding carbonyl compounds in the presence of TBHP. The allylic oxidation of alkene **1** was achieved with Cr(CO)$_6$ in an acetonitrile solution of 90% TBHP, gave the allylic oxidation product **2** in high yield (eq 1) [2].

Cr(CO)$_6$ (0.5 equiv)

90%TBHP (1.2equiv)
reflux, 18 h
acetonitrile

MeO$_2$C

1

MeO$_2$C =O

2   83%

eq 1
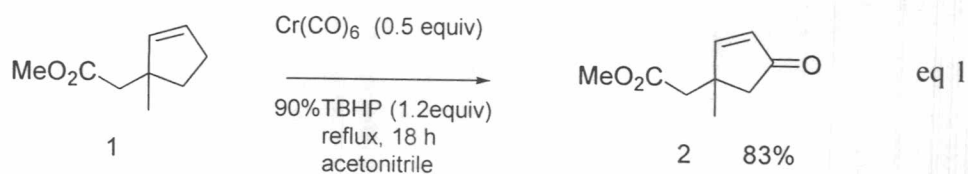
In addition, the presence of a secondary hydroxy functional group, this catalytic system selectively oxidizes an allylic methylene group **3** into α, β-unsaturated kenone in moderate yield (eq 2) **[2,3]**.

$$\text{eq 2}$$
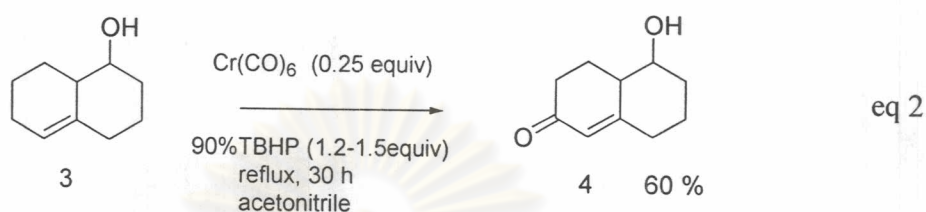
In the absence of double bonds, alcohols can be transformed to ketone as well (eq3) **[3]**.
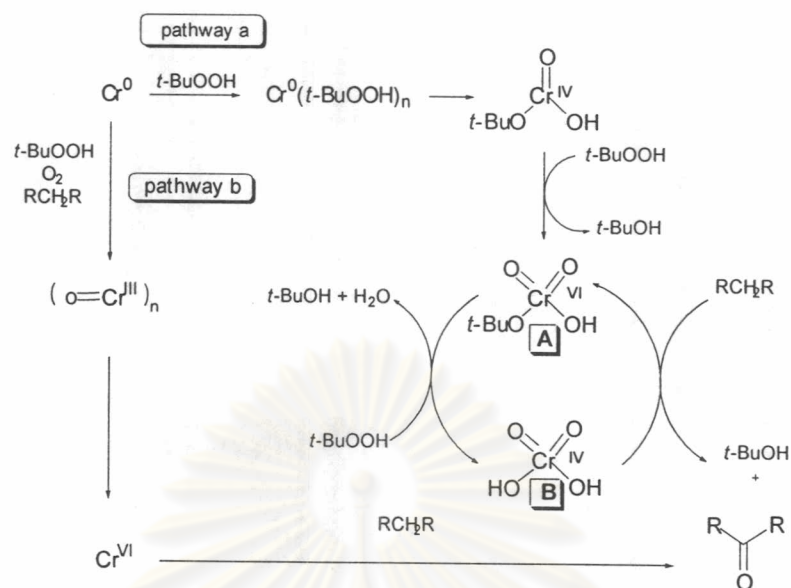

$$\text{eq 3}$$
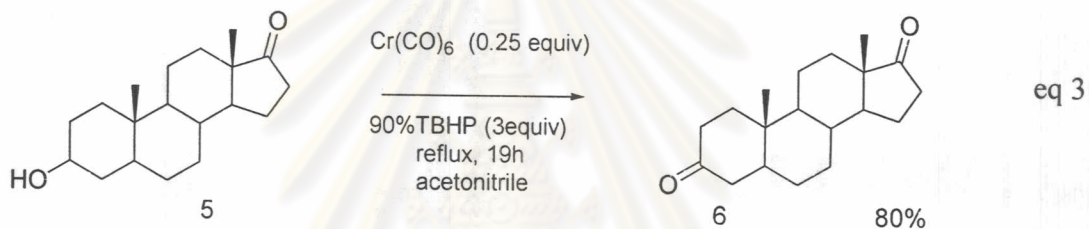
The benzylic oxidation of estrone derivatives **7** has also been oxidized to corresponding ketone **8** in moderate yield using this catalytic system in acetonitrile (eq 4) **[4]**.

$$\text{eq 4}$$
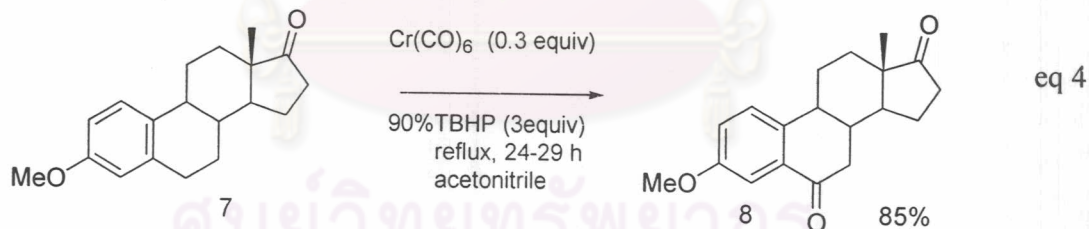
A possible mechanism for the oxidation of alkanes by Cr(CO)₆/TBHP has not been developed, but the reaction could be explained as shown in Scheme 1.1.

pathway a

Cr^0 $\xrightarrow{\text{t-BuOOH}}$ Cr^0(t-BuOOH)$_n$ $\longrightarrow$

$$\underset{t\text{-BuO}\quad\text{OH}}{\overset{\displaystyle O}{Cr^{IV}}}$$

t-BuOOH
O$_2$
RCH$_2$R

pathway b

(O=Cr^{III})$_n$

t-BuOOH

t-BuOH

t-BuOH + H$_2$O

$$\underset{t\text{-BuO}\quad\boxed{A}\quad\text{OH}}{\overset{\displaystyle O\quad O}{Cr^{VI}}}$$

RCH$_2$R

t-BuOOH

$$\underset{HO\quad\boxed{B}\quad OH}{\overset{\displaystyle O\quad O}{Cr^{IV}}}$$

t-BuOH +

RCH$_2$R

Cr^{VI} $\longrightarrow$

$$\underset{O}{\overset{\displaystyle R\diagdown\diagup R}{}}$$

Scheme 1.1 A possible mechanism for the oxidation of alkanes by Cr(CO)$_6$/TBHP

The initial step involves the complexation of TBHP with Cr(CO)$_6$. In the complex, an intraspheric oxidation of Cr^0 into the Cr^{VI} compound takes place, which is then the active alkyl peroxychromate species, **A**. The oxidation of the alkane by **A** yields the Cr^{IV} compound **B**; moreover, **A** is then regenerated from **B** mediated by TBHP.

1.2.2 Cr(CO)$_5$(MeCN)

This complex has been used as catalyst for benzylic oxidation with TBHP but its oxochromium is much less selectivity than Cr(CO)$_6$ [4].
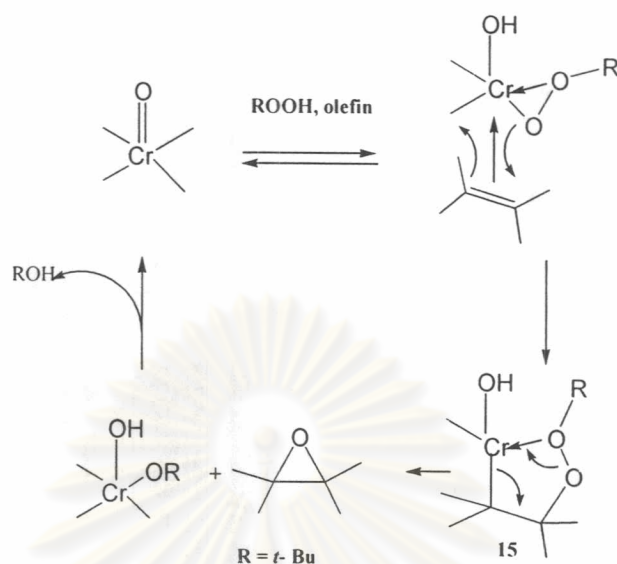
1.3 Chromium (III) as catalyst

There are several catalytic process involve chromium(III) as a starting catalysts. These complexes have been associated with oxygen gave oxochromium (IV) which showed to be effective oxidizing agents [1].

### 1.3.1 Tris (acetylacetonato), chromium Cr(acac)$_3$

The first use of tris(acetylacetonato)chromium as a catalyst for epoxidation of alkenes by TBHP [5]. The reactions resulted in regio- and stereospecific epoxides with

good yields at room temperature and low catalyst concentrations in the absence of oxygen (eqs 5-7).

9   Cr(acac)$_3$ / TBHP   10   28-100 %   eq 5

11   Cr(acac)$_3$ / TBHP   12   13-60 %   eq 6

13   *E* or *Z*   Cr(acac)$_3$ / TBHP   14   eq 7

trans epoxide from *E* - 51
cis epoxide from *Z* - 51

The enantiospecificity and high yields of the epoxidations imply a heterolytic concerted mechanism. The initial step involves a complex formation between the metal catalyst and TBHP [5,6] which gives rise to a peroxo-metal complex. Complexes of metals in low oxidation states are rapidly oxidized by hydroperoxides to their highest oxidation state. The olefin coordinates to the metal on a position adjacent to the peroxo ligand. The olefin-metal interaction is a pure Lewis acid/Lewis base association, since Cr^{VI} has no d electrons available for back-bonding to the olefin. The olefin, therefore, is expected to lose its nucleophilic nature upon coordination and become an electrophilic dipolarophile. This permits a nucleophilic attack *via* an intramolecular 1,3-dipolar cycloaddition of the O$_2^{2-}$ group to the olefin. The resulting five-membered peroxo-metallocyclic intermediate **15** then decomposes by 1,3-dipolar cycloreversion to produce the epoxide and an oxo-metal complex presented in Scheme 1.2.

Scheme 1.2 Epoxidation of olefin catalyzed by oxo-chromium complex

This mechanism is consistent with the π-σ rearrangement (*cis*-insertion) which occurs in most transition metal catalyzed transformations of olefins. In intramolecular cyclic and pseudocyclic peroxymetalations, the rate-determining step is generally the coordination of the olefin to the metal. This requires the presence on the metal of vacant coordination sites adjacent to the peroxide group. Recently, the efficient cleavage of the $CH_2=CH_2$ group of methacrylic acid esters, **16** was carried out with hydrogen peroxide and small amount of Cr (acac)$_3$ (eq 11) [7].

% conv. 96%
% selectivity 74%
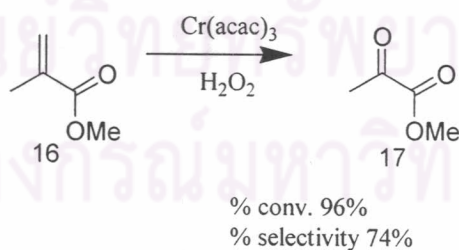
eq 8

1.3.2. Chromium carboxylate class, Cr(OOCR)$_3$

Chromium carboxylates have usaully been examined with the aim of obtaining soluble catalysts in organic substrates or solvents. The most considered being

chromium(III) stearate [8,9]. The chromium(III) acetate has been less investigated; where as, chromium(III) trifluoroacetate, chromium(III) naphthenate, chromium(III) octoate have been rarely used.

A. Chromium(III) stearate

Chromium(III) stearate has been employed to promote the autooxidation of alkanes, alkene, primary, secondary and benzylic carbons. Chromium(III) stearate used in conjunction with alkyl hydroperoxides has been examined as an oxidizing agent for transformation of alkanes and secondary alcohols at 80°C – 125°C (eqs 9 and 10) [8,9].
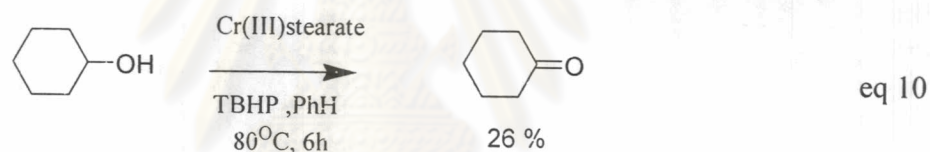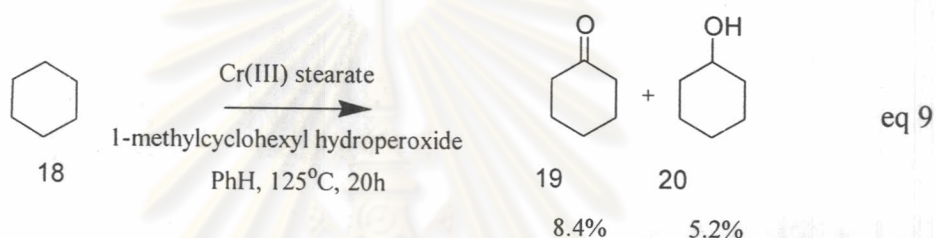
1.3.3 Chromium (III)Salen

These complexes have been mainly used as catalysts for oxidation of alkenes by PhIO [10,11]. Recently, the catalytic properties of $(salen)Cr(H_2O)_2Cl$ and $(salen)Cr(ONO)(H_2O)$ for oxidations with $NaNO_2$ under aerobic and anaerobic conditions have been examined. Cyclohexene was unreactive while the epoxidation of styrene, and stilbene were achieved in low yields with poor conversions, and with some cleavage of the double bond.
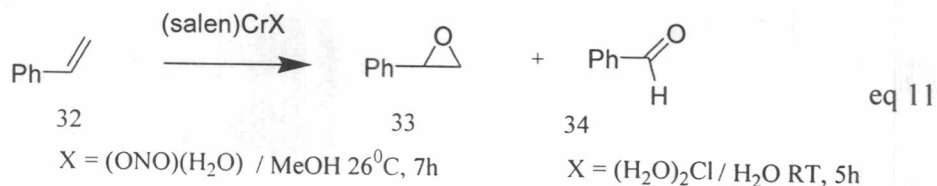
1.4 Chromium (VI) as catalyst

The association of a Cr(VI) complex with oxygen donor began while ago. The CrO_3 complex always has been used in chromium(VI)-catalyzed oxidation. The CrO_3/TBHP system oxidizes benzylic [12] (eq 4), allylic [13] and propargylic [14] carbons with fair yields at ambient temperature. The oxygenation of double bonds does occur when there are no more available allylic hydrogens. Oxidation of primary and secondary alcohols to carbonyl compounds was also catalyzed by this system. When peroxide was added to a solution of CrO_3 in dichloromethane, the metal oxide was solubilized and the solution turned into a red-purple color. This implies that the active oxidation catalyst is not CrO_3. A peroxochromium (VI) intermediate was ruled out [15]. A *tert*-butylperoxychromium (VI) complex (A) is seen as a reasonable intermediate. In the mechanism for the oxidation of alcohols, the formal oxidation state of Cr^{VI} is maintained throughout the catalytic cycle (Scheme 4) [16]. Interaction between A and the alcohol forms the alkoxy-*t*-butylperoxy-chromium intermediate B which evolves the carbonyl compound and *t*-BuOH in recycling CrO_3 as shown in Scheme 1.3.
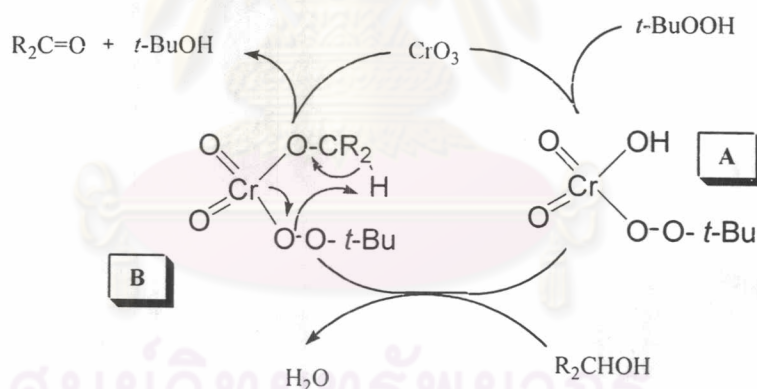
**Scheme 1.3** Chromium (VI)- catalyzed oxidation of alcohol

1.5 Oxidation of alcohol

Alcohols are a particularly important class of organic compounds because the hydroxyl functional group is transformed to other interesting functional groups. Oxidation of alcohols leads to ketones, aldehydes, and carboxylic acids. These functional groups undergo vast variety of additional reactions. Therefore, oxidation reaction of alcohols are some of the most important and common organic reactions.
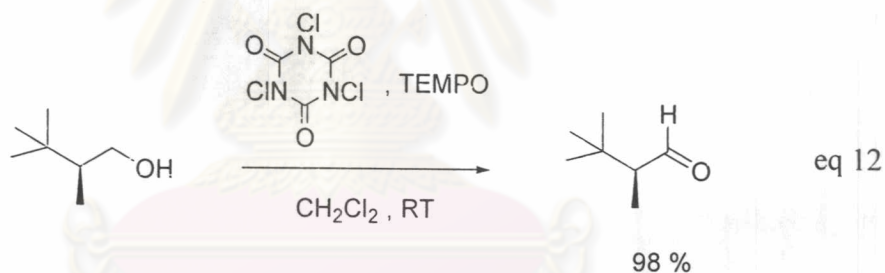
1.5.1 Oxidation of primary alcohol

Primary alcohol can be oxidized by various oxidants to aldehyde; however, it can be easily transformed further to give carboxylic acid.

primary alcohol   aldehyde   carboxylic acid
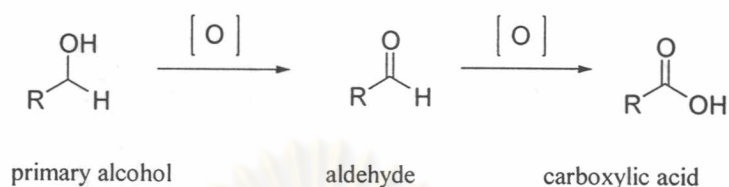
For these reasons, the selective oxidation of alcohols to corresponding aldehydes with no overoxidation to carboxylic acid has been studied. An efficient oxidation of primary alcohols to the corresponding aldehydes can be carried out at room temperature and in methylene chloride, using trichloroisocyanuric acid in the presence of catalytic TEMPO: Alcohol substrates are oxidized to the corresponding carbonyls in high yield and excellent chemoselectivity with out no overoxidation to carboxylic acids (eq 12) [17].


eq 12

98 %

1.5.2 Oxidation of secondary alcohol

Secondary alcohols are easily oxidized to give ketones by various oxidants.


secodary alcohol   ketone
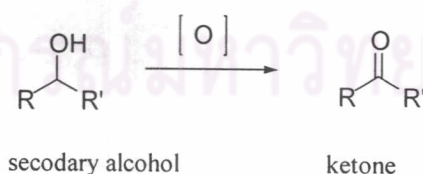
A mild and efficient oxidation of alcohols with o-iodoxybenzoic acid (IBX) catalyzed by β-cyclodextrin in a water/acetone mixture has been developed. A series of alcohols were oxidized at room temperature in excellent yields of carbonyl products (eq 13) [18].

eq 13
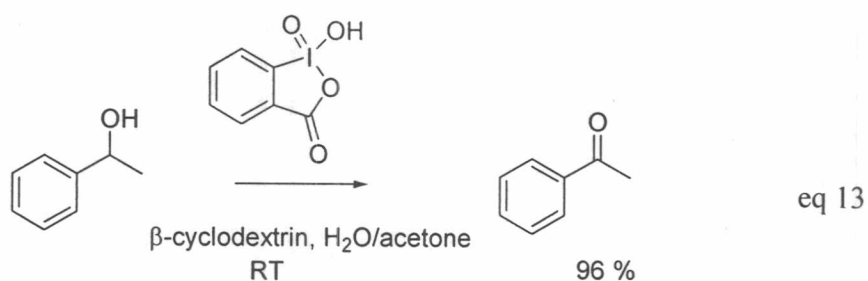
1.6 Oxidation of alkene

Addition of oxygen at carbon-carbon double bonds by high oxidation state metals such as permanganate ion and osmium tetroxide. Under mild condition potassium permanganate can convert alkene to diol compound. The cyclic mangaese ester is an intermediate in this oxidation that gives *cis*-diol after basic hydrolysis (eq 14).

eq 14

cis-diol
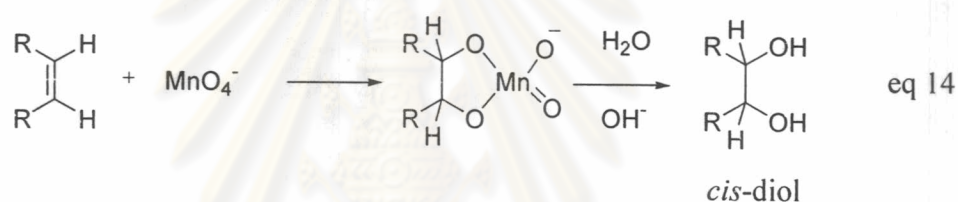
However, potassium permanganate is capable of further oxidizing diol with cleavage carbon-carbon bond under vigorous condition. It is also possible to employ permanganate oxidation in organic solvents by using phase transfer agents. Studies with cyclododecene present that mixture of carboxylic acid, diones, ketols and diol were obtained but that the ratio of the various products could be effected by the amount of oxidant loaded (eq 15) [19].


eq 15
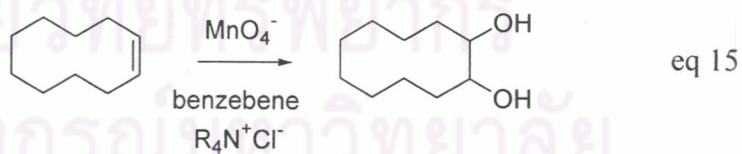
Osmium tetroxide is a highly selective oxidant giving a stereospecific addition affords *cis*-diol (eq 16) [20].


eq 16
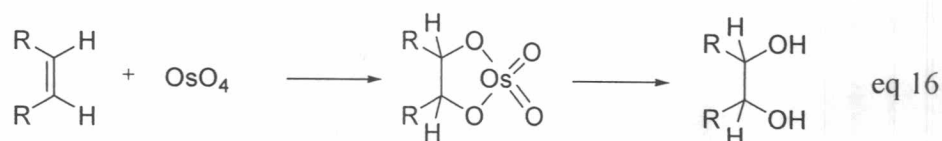
This reagent is expensive; however, this drawback can be overcome by procedures that use a catalytic amount of osmium tetroxide.

1.7 Oxidation of allylic position

Carbon-carbon bonds, besides being sensitive to addition of oxygen or cleavage, can also react at allylic positions. Among the transition metal oxidants, chromium reagent is the most satifactory for allylic oxidation (eq 17) [21].

eq 17
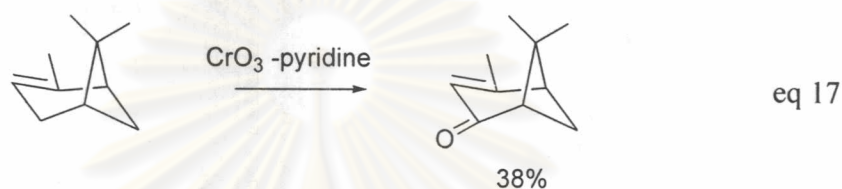
The heterogenous catalyst, chromium aluminophosphate-5 (CrOAP-5) by using *tert*-buthyl hydroperoxide (TBHP) as oxidant was used in place of pyridine has also found to be effective for allylic oxidation to corresponding α,β-unsatusated carbonyl compound (eq 18) [22].

eq 18
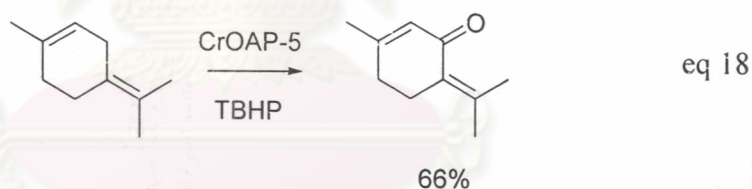
There are several species of mechanistic evidence elucidative that allylic radicals or cations are intermediates in these oxidations. Thus, ^{14}C in cyclohexene ring is distributed in the product cyclohexanone in a manner indicating that a symmetrical allylic intermediate is involved at the same state [23].
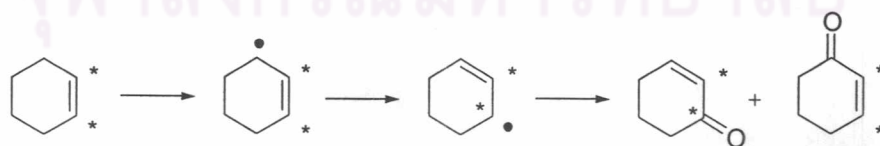
1.8 Literature review on chromium catalyzed oxidation of organic substrates

There are several catalytic systems that could provide excellent yield of desired product with good selectivity, particularly these catalyzed by chromium complexes as the catalyst in oxidation reaction.

Recent reports on chemical literatures found that numerous catalytic oxidation systems have received intensive interest and have been developed. Those systems were usually used chromium complexes as a catalyst in the presence of various oxidants in organic solvents as the reaction media.

In 1988 and 1989, Pritzkow and co-workers reported the first use of various metal catalysts including chromium (III) stearate in order to catalyze oxidation of hydrocarbons and alcohols to carbonyl compound in the presence of various oxidizing agents; 1-methylcyclohexyl hydroperoxide, TBHP, hydrogen peroxide, oxygen and air. These products were believed to derive from the decomposition of alkyl hydroperoxide [8,9].

In 1999, Muzart and his co-workers further reported the use of chromium trioxide catalyzed oxidation of allylic alcohol to aldehydes by using TBHP and cumyl hydroperoxide as oxidants. It was observed that TBHP showed a higher performance oxidant [24].

In 2000, Adam and his colleagues reported the use of catalytic amount of chromium(III) salen complex mediated selective oxidation of various alcohols to carbonyl compounds in the presence of iodozobenzene as the oxygen source. The reaction was carried out under mild condition. Allylic alcohols with fully substituted double bonds gave an appreciatable amount of epoxides besides the C-H oxidation products enones, while saturated alcohols were less readily oxidized [25].

In 2001, Chaudhuri and co-workers present tetramethylammonium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$, (DmpzHFC), a new oxidizing agent. It was prepared from chromium trioxide, 3,5-dimethylpyrazole and the solution of HF. It was found that the yield of product was high but the reagent have to apply in stoichiometric amount [26].

In 2002, Lou and Xu developed a new catalytic process using chromium trioxide in the absence of extra solvent. It was observed that primary alcohols were transferred into aldehydes in high yield and good selectivity [27].

In the same period, Fuchs and Lee reported the chemospecific oxidation of C-H bonds at $-40^{\circ}C$ catalyzed by chromium(VI) complex using periodic acid as oxidant and acetic anhydried as solvent. The substrate could be functionalized to alcohols in moderate to high yield with good selectivity [28]. In addition, Songsangcharoen reported the use of transition metal complexes catalyzed oxidation of cyclohexane to cyclohexanone with various oxidants. Chromium(III) stearate was the appropriate catalyst for cyclohexane oxidation using TBHP as oxidant [29].

In 2003, Xu and Trudell reported the use of catalytic amount of chromium (III) acetylacetonate, [Cr(acac)$_3$] catalyzed oxidation of alcohols with periodic acid using acetonitrile as a solvent. It observed that alcohols were converted to aldehydes and ketone in excellent yield. The reaction was conducted at room temperature and the reaction time required was short [30].

This research focuses on the development of selective catalytic oxidation of natural product substrates such as α-pinene, α-ionone, β-ionone, menthol, cholestanol, cinnamyl alcohol, α-terpinene, γ-terpinene and so on, These can be oxidized into their corresponding oxygenated compounds which are the important precursors for a number of pharmaceutical, perfumery and food industries.

1.6 The goal of this research

The purposes of this research can be summarized in the following task.

1. To prepare and characterize chromium stearate complexes.
2. To study the optimum conditions for model substrates by using chromium catalysts.
3. To apply the optimum condition to use for oxidation of natural product substrates.
4. To study the chemo- and regioselectivity of the developed catalytic oxidation system